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Inherited Unbalanced Subtelomeric Translocation in a Child With 8p- and Angelman Syndromes

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A 10 1/2-month-old boy was found to have an unbalanced karyotype, 45,XY,der(8)t(8;15)(p23.3;q13). One of 83 analyzed cells also contained an unidentified small marker. Fluorescence in situ hybridization (FISH) using cosmid probes for SNRPN, D15S10, and GABRB3 for the Prader-Willi syndrome (PWS)/Angelman syndrome (AS) critical region were not present on the derived chromosome. The child had some physical findings compatible with monosomy 8p. The mother also was a balanced carrier for the translocation. She also had 2/80 cells with an additional small marker chromosome, similar in size to the extra chromosome in the one cell of the propositus. FISH using an 8 paint did not show the reciprocal exchange on the der(15) but was demonstrated by using an 8p telomeric probe. At 18 months of age the child has some manifestations of AS. Earlier diagnosis may have been masked by the 8p- phenotype, or related to difficulty in diagnosing AS in infants. Am. J. Med. Genet. 70:150–154, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: chromosomal translocation; telomere; Angelman syndrome; fluorescent in situ hybridization

INTRODUCTION

Approximately 70% of PWS and AS patients have a 15q11q13 deletion with about 5% of cases due to unbalanced translocations [Reeve et al., 1993], many of which involve loss of proximal 15q translocated to the terminal end of other chromosomes [Jauch et al., 1995]. Rivera et al. [1990] reviewed 33 previously published PWS cases with translocations of which 27 had an unbalanced karyotype with 45 chromosomes involving a translocation of proximal 15q to the telomere of a reciprocal chromosome. Among these cases, 1 of 19 informative cases were inherited and the rest were de novo events. More recently, 9 of 11 reported cases were informative for origin in which two were inherited [Table I; Smith et al., 1991; Smeets et al., 1992; Park et al., 1992; Rossi et al., 1993; Reeve et al., 1993; Smith et al., 1994; Jauch et al., 1995; Wenger and Cummins, 1995], the latter resulting in AS due to uniparental disomy [Smeets et al., 1992; Smith et al., 1994]. Several cases were evaluated for the presence of telomeric sequences on the reciprocal chromosome. Five cases of PWS were found to have the telomeric sequences located interstitially on the derived chromosome [Park et al., 1992; Rossi et al., 1993; Reeve et al., 1993]. One case of PWS and two cases of AS showed loss of the telomere from the reciprocal chromosome [Smith et al., 1994; Jauch et al., 1995]. We report on a patient with der(8)t(8;15)(p23.3;q13) who was maternally inherited with loss of the 8p telomere on the derived chromosome.

CLINICAL REPORT

At age 8 months, the propositus was severely developmentally delayed. All body measurements were at or below the 3rd centile. During neurological examination he could roll but could not sit or hold his own bottle. He was just beginning to babble; his eyes did not track. He had premature closure of one lambdoidal suture and plagiocephaly on CT scan.

At 10 months, an MRI scan of the brain demonstrated small optic nerves, small optic chiasm, diminished optic radiation myelination consistent with hypoplasia, and mild diffuse cerebral atrophy vs. hypoplasia. At age 11 months, EEG showed interictal epileptiform pattern with intermixed generalized spike and wave discharges.

At 18 months, height, weight, and head circumference were all at or below the 5th centile. He had light red hair, protruding ears, wide smile, and spastic movements. He was severely mentally retarded. His mother reported that he is always happy and has never cried. Repeat EEG showed atypical absence seizures accompanied by slow spike and wave activity and

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TABLE I. Translocations Resulting in PWS or AS*

45,XX,−3,−15,+der(3)t(3;15)(q29;q13)de novo	Wenger and Cummins, 1995
45,XY,−5,−15,+der(5)t(5;15)(qter;q13)	Park et al., 1992
45,XX,−5,−15,+der(5)t(5;15)(qter;q13)de novo	Rossi et al., 1993
45,XX,−6,−15,+der(6)t(6;15)(p25.3;q11.1)pat UPD	Smeets et al., 1992
45,XX,−7,−15,+der(7)t(7;15)(q36;q13)	Jauch et al., 1995
45,XY,−8,−15,+der(8)t(8;15)(p23.3;q11)pat UPD	Smith et al., 1994
45,XY,−8,−15,+der(8)t(8;15)(p23.3;q13)mat	Present case
45,XY,−9,−15,+der(9)t(9;15)(q34;q13)de novo	Smith et al., 1991
45,XY,−9,−15,+der(9)t(9;15)(qter;q11.1)de novo	Rossi et al., 1993
45,XY,−10,−15,+der(10)t(10;15)(q26;q13)de novo	Jauch et al., 1995
45,XX,−12,−15,+der(12)t(12;15)(qter;q13)de novo	Reeve et al., 1993
45,XX,−12,−15,+der(12)t(12;15)(qter;q11.1)de novo	Rossi et al., 1993

*Cases reported after Rivera et al. [1990], review.

atonic seizures manifest as head drops. He has not begun to walk.

Regarding family history (Fig. 1), the normal mother (III-2) has a normal brother (III-4) and an institutionalized sister (II-3) who is described by the family as having a happy disposition, laughter, and no speech, but to date has not been studied cytogenetically. The maternal grandmother (II-2), who is phenotypically normal, has normal half-sibs.

MATERIALS AND METHODS

Heparinized blood samples on propositus, mother, and maternal grandmother were cultured and harvested using routine cytogenetic technique. The cells were trypsin G-banded and karyotyped.

To further delineate the karyotype, FISH probes (ONCOR) for SNRPN, D15S10, GABRB3, 8 paint, 8p telomere, 15 paint, and 15 classical satellite were used following manufacturer's instructions. Freshly made slides were denatured prior to overnight probe hybridization at 37°C. Probes were detected with FITC and counterstained with propidium iodide. The slides were viewed with a fluorescent microscope using a dichroic filter and photographed with Ektachrome film.

RESULTS

The patient's karyotype was 45,XY,der(8)t(8;15)(p23.3;q13)mat (Fig. 2). SNRPN, D15S10, and GABRB3 were present in one copy on the patient's normal 15, and 2 copies in the mother's cells; the normal 15 and the der(15). Therefore, the breakpoint on 15 defined by FISH was distal to the GABRB3 probe in the PWS/AS critical region. The mother's karyotype was 46,XX,t(8;15)(p23.3;q13)mat (Fig. 3) and the maternal grandmother's karyotype was 46,XX,t(8;15)(p23.3;q13). A FISH paint for chromosome 8 identified the normal 8 and der(8) but did not confirm the reciprocal translocation on the der(15) in the mother's cells (Fig. 4). An 8p telomere probe did bind to the normal 8 and the der(15) (Fig. 5), which suggested that a small amount of chromosome 8 material was on the der(15) reciprocal translocation. This demonstrates limitations to the use of whole chromosome paints for detecting small rearrangements [Gould et al., 1992]. Both the patient and his mother had one or two marker chromosomes among the 83 or 80 cells analyzed, respectively. The acrocentric marker was half the size of the der(15). Chromosome 15 paint on the patient's G-banded metaphase with marker identified the normal 15, derived 8, but not the marker, which may be due to the extremely small size of the marker, or uninvolvement of chromosome 15. A classical satellite FISH probe for 15 was used on at least 200 interphase cells from the patient and his mother to determine if the marker was derived from 15, but results on both were within background, most likely due to its low frequency. It was not possible to obtain a skin biopsy to look for tissue limited mosaicism.

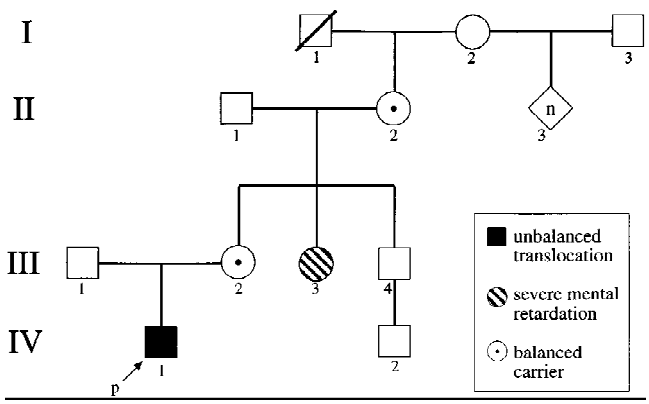

Fig. 1. Pedigree of proband's family.

DISCUSSION

At age 10 months, the child had some characteristics suggestive of monosomy 8p syndrome, including microcephaly, failure to thrive, growth and mental retardation, and malformed ears. The karyotype suggested that the child should also have characteristics of AS; however, AS can be difficult to diagnose in a child under 2 years of age [Buntinx et al., 1995], and some of the patient's clinical findings overlap both of these syndromes. The karyotype therefore provides information for predicting development of Angelman syndrome characteristics in the patient, as observed at 18 months, including wide smile, happy disposition, spastic movements, and epilepsy.

Jauch et al. [1995] have reported that many unbalanced karyotypes resulting in PWS or AS involve the telomeric region of the reciprocal chromosome [Rivera et al., 1990; Table I]. The unbalanced cases had 45

Fig. 2. Karyotype of proband: 45,XY,+der(8)t(8;15)(p23.3;q13).

chromosomes with the reciprocal chromosome breakpoint at the most distal band. This suggests that breakpoints occurring at telomeres are more likely to result in 3:1 segregation with loss of the small derived chromosome [Rivera et al., 1990] or result in uniparental disomy [Smeets et al., 1992; Smith et al., 1994]. Most of these cases have been de novo, although a few have been inherited [Rivera et al., 1990; Smeets et al., 1992; Smith et al., 1994; present case]. Cases examined for telomeric sequences have identified five cases with PWS in which the breakpoints were distal to the telomere [Park et al., 1992; Rossi et al., 1993; Reeve et al., 1993], and one case with PWS and three cases with AS have demonstrated the breakpoint proximal to the telomere on the reciprocal chromosome [Smith et al., 1994; Jauch et al., 1995; present case].

The involvement of telomeric regions in the translocations may suggest instability at these regions. Palin-

Fig. 3. Karyotype of proband's mother: 46,XX,t(8;15)(p23.3;q13).

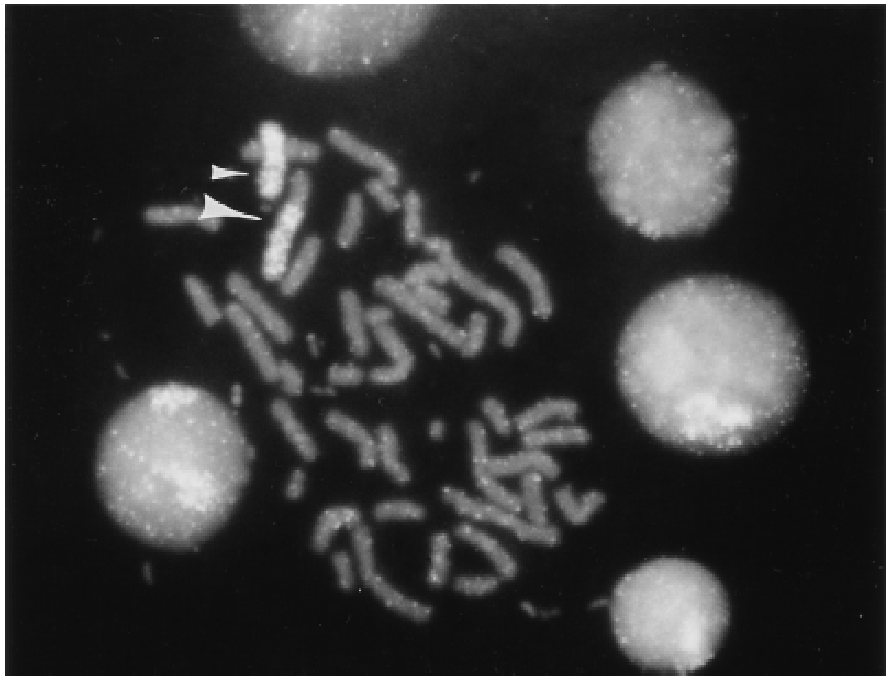

Fig. 4. Chromosome 8 FISH paint on mother's metaphase. The probe identifies the normal 8 (small arrowhead) and the der(8) (large arrowhead), but not the der(15).

dromic sequences have been suggested to be at telomeric regions [Cavalier-Smith, 1994]. Similar interstitial sequences to the telomeric regions have been suggested to result in recombinogenic properties [Hastie and Allshire, 1989]. The telomeric translocations found in PWS and AS suggest that repetitive sequences within the PWS/AS critical region may be similar to sequences present within the telomeric regions of chromosomes.

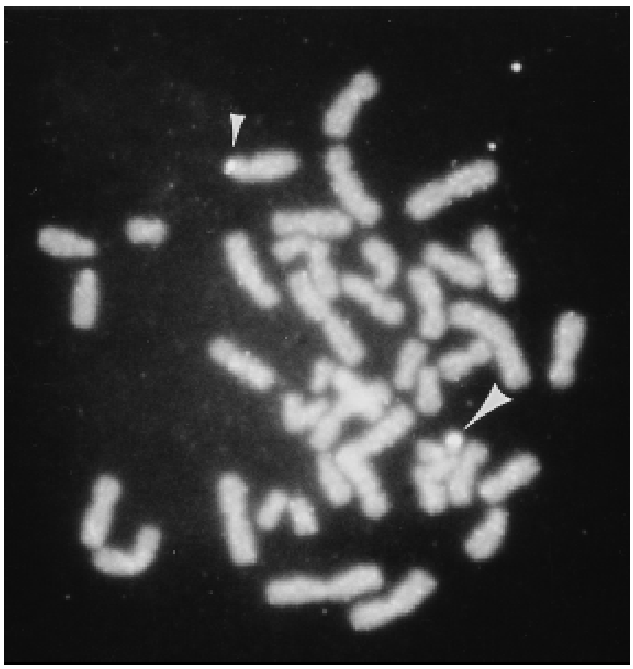

Fig. 5. An 8p telomere FISH probe on mother's metaphase. The probe signals identify the normal 8 (small arrowhead) and der(15) (large arrowhead).

Because telomeric translocations have identified terminal involvement as well as subtelomeric rearrangements, it may be of clinical importance to distinguish between the two, since a subtelomeric translocation, with loss of the derived chromosome, may involve loss of reciprocal chromosomal material and therefore manifest other phenotypic abnormalities.

NOTE ADDED IN PROOF

A peripheral blood sample was received on the mother's sister (III-3). Her karyotype is 45,XX,der(8)t(8;15)(p22.3;q13)mat.

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